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EXAMINER	
ZARA, JANE J	

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1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/553,001	GILCHREST ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 December 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-82* is/are pending in the application.

4a) Of the above claim(s) *1-77* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *78-82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12-15-09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 12-15-09.

Claims 1-82 are pending in the instant application.

Election/Restrictions

This application contains claims 1-77, drawn to an invention nonelected with traverse in the reply filed on 4-29-09. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Sequence Compliance Notice

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. **Please provide an appropriate SEQ ID No. for the sequence recited in claim 81, and any other places as appropriate in the specification.**

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections/Rejections Necessitated by Amendments

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 78-82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hitoshi et al (US 2002/0027167) in view of Norton et al (Nature Biotech., Vol. 14, pages 615-619, 1996)) (See Document C45, IDS filed 4-17-09) and Page et al. (Exp'l. Cell Res., Vol. 252, pages 41-49, 1999) (See Document C48, IDS filed 4-17-09) for the reasons of record set forth in the Office action mailed 8-15-09 and for the reasons set forth below.

The claims are drawn to compositions comprising an oligonucleotide comprising between 1-20 increments of TTAGGG, optionally comprising GTTAGGGTTAG, or

comprising at least 50% identity with these motifs, wherein the first nucleotide linkages on the 3'-end are hydrolyzable by a 3'-5' nuclease, and which oligonucleotide further comprises non-hydrolyzable linkages, which are optionally phosphorothioate internucleotide linkages.

Hitoshi et al (US 2002/0027167) teach nucleic acids encoding the nuclease MRE11, recombinant MRE11, various biochemical assays monitoring its nuclease activity, its involvement in repairing DNA and chromosomal end-breaks, checkpoint regulation, cell cycle regulation and proliferative diseases. Hitoshi teaches methods of screening for modulators of MRE11 activity using synthesized substrates in various in vitro assays, and the motivation to screen for modulators of MRE11 activity as therapeutic candidates for modulation of cellular proliferation. Hitoshi also teaches the lethality of chromosomal breaks to cells, and the motivation to search for compounds that enhance the sensitivity of a cell to chemotherapeutic agents, where modulators of MRE11 are screened as useful therapeutics in cancer, inflammation and other diseases involving cellular proliferation. Hitoshi teaches the binding of MRE11 polypeptide to RAD50 and/or NSB1, and subsequent nuclease activity of MRE11 on oligonucleotides, as well as methods of screening for inhibitors of MRE11 nuclease activities, and inhibitors MRE11/RAD50/NSB1 interactions (see esp. abstract, pages 1-5, 11-13, figures 27-33; claims 1-18).

Hitoshi does not teach the synthetic substrate sequences and the modifications instantly claimed.

Page et al. (Exp'l. Cell Res., Vol. 252, pages 41-49, 1999) teach compositions comprising a choice of various oligonucleotides with at least one increment of an oligonucleotide with at least 50% sequence identity with TTAGGG, which oligonucleotides also comprise non-hydrolyzable phosphorothioate internucleotide linkages for stability from nuclease degradation, and which oligonucleotide sequences are known to populate the 3' termini overhang of chromosomes (*a.k.a.* telomere overhang), and which 3' terminal overhangs are associated with high telomerase activity in immortal cells, transformed cells, mitogenic stimulation and proliferative diseases. Page teaches the inhibition of telomerase in a non-sequence manner using phosphorothioate oligonucleotides, and the cytotoxicity of phosphorothioate oligonucleotides (see entire document, esp. the text on p. 41, second full paragraph on p. 42, Tables 1, 2 and Figures 1, 2 on pages 42-43)) (See Document C48, IDS filed 4-17-09)

Norton et al (Nature Biotech., Vol. 14, pages 615-619, 1996)) (See Document C45, IDS filed 4-17-09) teach compositions comprising an oligonucleotide comprising between 1-20 increments of TTAGGG, including GTTAGGGTTAG, which oligonucleotide is optionally a PNA or comprises phosphorothioate internucleotide linkages (see esp. Table 1 on page 616 and third full paragraph on page 618).

It would have been obvious to one of skill in the art to design and use the oligonucleotides instantly claimed to measure MRE11 nuclease activity because MRE11 was well known in the art to have 3'-5' exonuclease activity and to be involved in repairing DNA strand breaks and to be involved in the regulation of telomerase

activity and in cell cycle regulation, as taught previously by Hitoshi et al, and the motifs instantly claimed were all well known motifs existing as 3' telomerase overhangs, as taught previously by Page and Norton and many others in the field. One would have been motivated to design the oligonucleotides claimed, including the incorporation of stabilizing modifications in the internal internucleotide linkages, as substrates to measure MRE11 exonuclease activity because the modifications claimed and the substrates claimed were taught previously by Norton and Page, phosphorothioate internucleotide linkages were well known to be stable to nuclease degradation, and placing completely resistant linkages on the termini of the substrates would preclude the ability to measure exonuclease activity, since phosphorothioate oligonucleotides were known to inhibit telemerase activity and therefore would preclude the ability to screen for other inhibitors of the process, such as exonuclease activity of MRE11. One also would have been motivated to provide the substrate analogs instantly claimed, with cleavable linkages at the termini, and non cleavable linkages in the interior of the analogs, in order to allow for the assembly of MRE11/RAD50/NSB1 complexes, and more specifically screen for modulators of the exonuclease activity while being able to measure the presence of partial exonuclease activity upon detection of removal of some or all of the hydrolysable, terminal bases.

After all, the presence of completely phosphorothioated residues on the substrate analogs would preclude the ability to measure any exonuclease activity of the substrate analogs, since phosphorothioate internucleotide linkages are known to be resistant to exonuclease activity and therefore would not be removed by MRE11, while the

complete absence of exonuclease resistant linkages would allow for the complete removal of all nucleobases in the presence of functional MRE11. One of skill in the art would reasonably expect then, that internally resistant linkages, as instantly claimed, would allow a fine tuning in determining the ability of potential modulators to inhibit MRE11 exonuclease activity, as well as providing an assay to measure the assembly of the MRE11/RAD50/NSB1 complex on the substrate analog.

One would have reasonably expected that placing these modifications onto the substrates instantly claimed (e.g. internal linkages to comprise phosphorothioate linkages) would provide for appropriate substrates with which to monitor the 3-5' exonuclease activity of MRE11, without fully degrading the substrates. This design therefore would be reasonably expected to be suitable for measuring the exonuclease activity of MRE11 in vitro, and to be suitable in an assay to search for modulators of MRE11 in order to study the role of MRE11 exonuclease activity in various cellular and pathological processes, including chromosomal repair, cellular senescence, proliferative disorders, and disorders reflecting the imbalance of telomerase and MRE11 activities.

For these reasons, the instant invention would have been obvious to one of skill in the art at the time of filing.

Applicant's arguments filed 12-15-09 have been fully considered but they are not persuasive. Applicant argues that the teachings of Page do not render the instant invention obvious because Page teaches oligonucleotides that are fully MRE11 exonuclease resistant, while the instant invention claims substrate oligonucleotides that are both non-resistant (3' terminal residues) and resistant (internal residues).

Contrary to Applicant's assertions, the combined teachings of Hitoshi, Norton and Page together render the instant invention obvious.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

As stated in the 103 rejection above, and reasonably relying on the teachings of Hitoshi, page and Norton, one would have been motivated to provide the substrate analogs instantly claimed, with cleavable linkages at the termini, and non cleavable linkages in the interior of the analogs, in order to allow for the assembly of MRE11/RAD50/NSB1 complexes, and more specifically screen for modulators of the exonuclease activity while being able to measure the presence of partial exonuclease activity upon detection of removal of hydrolysable, terminal bases. After all, the presence of completely phosphorothioated residues on the substrate analogs would preclude the ability to measure any exonuclease activity of the substrate analogs, since phosphorothioate internucleotide linkages are well known in the art to be resistant to exonuclease activity and therefore would not be removed by MRE11. On the other hand, the complete absence of exonuclease resistant linkages would allow for the complete removal of all nucleobases in the presence of functional MRE11. One of skill in the art would reasonably expect then, that internally resistant linkages, as instantly claimed, would allow a fine tuning in determining the ability of potential modulators to

inhibit MRE11 exonuclease activity, as well as providing an assay to measure the assembly of the MRE11/RAD50/NSB1 complex on the substrate analog.

For these reasons, the instant rejection is maintained.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is 571-273-8300. NOTE: If Applicant does submit a paper by fax, the original

signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jane Zara whose telephone number is (571) 272-0765. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fereydoun G. Sajjadi, can be reached on (571) 272-3311. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
3-23-10

/Jane Zara/

Primary Examiner, Art Unit 1635